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ORIGINAL ARTICLE

Stroke volume-directed administration of hydroxyethyl starch (HES 130/0.4) and Ringer's acetate in prone position during neurosurgery: a randomized controlled trial

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Abstract
Purpose General anesthesia in the prone position is associated with hypotension. We studied stroke volume (SV)-directed administration of hydroxyethyl starch (HES 130 kDa/0.4) and Ringer's acetate (RAC) in neurosurgical patients operated on in a prone position to determine the volumes required for stable hemodynamics and possible coagulatory effects.
Methods Thirty elective neurosurgical patients received either HES ($n = 15$) or RAC ($n = 15$). Before positioning, SV measured by arterial pressure waveform analysis was maximized by fluid boluses until SV did not increase more than 10 %. SV was maintained by repeated administration of fluid. RAC 3 ml/kg/h was infused in both groups. Thromboelastometry assessed coagulation. Mann–Whitney *U* test, Wilcoxon signed-rank test, ANOVA on ranks, and a linear mixed model were applied.
Results Comparable hemodynamics were achieved with the mean cumulative (SD) boluses of HES or RAC 240 (51) or 267 (62) ml ($P = 0.207$) before positioning, 340 (124) or 453 (160) ml ($P = 0.039$) 30 min after positioning, and 440 (229) or 653 (368) ml at the end of surgery ($P = 0.067$). The mean dose of basal RAC infusion was 813 (235) and 868 (354) ml ($P = 0.620$) in the HES and RAC group, respectively. Formation and maximum strength of the fibrin clot were decreased in the HES group. Intraoperative blood loss was comparable between groups ($P = 0.861$).
Conclusion The amount of RAC needed in the prone position was 25 % greater. The cumulative dose of 440 ml HES induced a slight disturbance in fibrin formation and clot strength. We suggest cautious administration of HES during neurosurgery.

Keywords Fluids · Hydroxyethyl starch · Neurosurgery · Prone position · Thromboelastometry

Introduction

The prone position is used for spinal procedures, including cervical, thoracic, and lumbar laminectomy and fusion, as well as parietal, occipital, and suboccipital craniotomy [1]. Anesthesia in the prone position is associated with significant hemodynamic alterations, such as decrease in arterial pressure [2] and cardiac index (CI) [3]. Optimization of cardiac function using perioperative goal-directed fluid administration reduces the length of hospital stay and complications after major surgery [4, 5]. In animals, goal-directed colloid administration also increases microcirculatory blood flow [6]. Colloid solutions have good plasma-expanding properties, but they carry a risk for coagulation disturbances [7]. Rapidly degradable hydroxyethyl starch (HES) is a suitable volume expander in the routine perioperative setting because of the low risk of hemostatic alterations [7]. In neurosurgery, normal coagulation capacity is of particular importance to prevent bleeding

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complications [8]. Data on the optimal fluid management for the neurosurgical patient in the prone position are lacking. To determine the volumes of HES and Ringer's acetate (RAC) required for stable hemodynamics, this study examined the stroke volume-directed administration of fluids in the prone position during neurosurgery. Possible effects on coagulation were studied with thromboelastometry.

Materials and methods

Adult patients scheduled for elective primary neurosurgery in the prone position at the Helsinki University Central Hospital (Töölö Hospital) were included in the study. Ethical approval for this study (Ethics Committee Number 13/13/03/04/09 HUS) was provided by the Ethics Committee for Surgery of the Hospital District of Helsinki and Uusimaa, Helsinki, Finland, and the National Agency of Medicines in Finland accepted the study protocol (EudraCT Ref. No 2009-009893-28). All patients gave their written, informed consent to participate in the study. Patients aged less than 18 years, with body mass index (BMI) greater than 36 (kg m^{-2}), congestive heart failure other than sinus rhythm, renal failure (*P* creatinine >120 μmol/l), hepatic failure, anemia (Hb <100 g/l), and thrombocytopenia (Pc $<100 \times 10^9$/l) were excluded.

Patients were premedicated with oral diazepam 5–20 mg. Preoperative antihypertensive medications were administered on the morning of surgery, except for angiotensin-converting enzyme inhibitors and angiotensin II antagonists. Patients were allowed to eat and drink normally up to 6 h before the surgery. Before the induction of anesthesia a basal infusion of Ringer's acetate (RAC) was started at a rate of 3 ml/kg/h to all patients. All patients were given preoperative antibiotics (cefuroxime/vancomycin). Anesthesia was induced in the supine position with fentanyl 2–6 μg/kg and either thiopental 2–7 mg/kg or propofol 2–3 mg/kg. All patients received glycopyrrolate 0.2 mg. Rocuronium (0.5–0.9 mg/kg) was used for muscle relaxation. Boluses of fentanyl and rocuronium were given during the anesthesia. Anesthesia was maintained with sevoflurane (1 MAC) in a mixture of nitrous oxygen and air, or a continuous infusion of propofol (4–10 mg/kg/h) and remifentanil (0.125–0.25 μg/kg/h). The patients were tracheally intubated and mechanically ventilated using volume-controlled ventilation with a tidal volume of 8–10 ml/kg body weight at a rate of 10–15/min for normoventilation (target $PaCO_2$, 4.5–5.0 kPa). Positive end-expiratory pressure (PEEP) was not applied.

Routine monitoring was commenced, including noninvasive arterial pressure, ECG (lead II), and arterial saturation of oxygen (SpO_2), and after intubation of the trachea and the start of mechanical ventilation, nasopharyngeal temperature, spirometry (Side stream®; Datex-Ohmeda, GE Healthcare, Madison, WI, USA), end-tidal concentration of carbon dioxide ($ETCO_2$), and inhaled anesthetics. After the induction of anesthesia, an 20 G arterial catheter (Becton Dickinson, Temse, Belgium) was inserted into the left or right radial artery for invasive monitoring of arterial pressures and to obtain blood samples. A pressure transducer (FloTrac®; Edwards Lifesciences, Irvine, CA, USA) was connected to the radial arterial line and to the Vigileo® System (Edwards Lifesciences) with software ver. 3.02. The device enables continuous monitoring of cardiac output (CO) by pulse contour analysis without external calibration. The system provides CO, cardiac index (CI), stroke volume (SV), stroke volume index (SVI), and stroke volume variation (SVV).

The following parameters were monitored continuously during the study period: systolic arterial pressure (SAP), mean arterial pressure (MAP), diastolic arterial pressure (DAP), heart rate (HR), CO, CI, SV, SVI, SVV, $ETCO_2$, and SpO_2. Urine output and fluid balance were registered at predetermined intervals. During data recording, ventilatory settings were kept constant.

Invasive arterial blood pressure was measured at the level of the heart, and the target MAP was 60 mmHg or higher. Boluses of phenylephrine (0.05–0.1 mg) or ephedrine (5–10 mg) were given if MAP was less than 60 mmHg. A phenylephrine infusion was started whenever MAP remained below 60 mmHg for more than 5 min.

In a random order (using closed envelopes drawn in sequential order by the primary investigators), the patients were allocated in blocks of three to receive one of the following study solutions:

1. 6 % HES solution (Voluven®; 60 mg/ml, average molecular weight 130 kDa, molar substitution ratio 0.4, pH 4.0–5.5, content Na^+ 154 mmol l^{-1}, Cl^- 154 mmol l^{-1}; Fresenius Kabi, Bad Homburg, Germany) (HES group, $n = 15$)
2. Ringer's acetate solution (Ringer acetate®, pH 6.0, content Na^+ 131 mmol l^{-1}, Cl^- 112 mmol l^{-1}, K^+ 4 mmol l^{-1}, Ca^{2+} 2 mmol l^{-1}, Mg^{2+} 1 mmol l^{-1}, CH_3COO^- 30 mmol l^{-1}; Fresenius Kabi, Bad Homburg, Germany) (RAC group, $n = 15$).

In the supine position, after the induction of anesthesia, patients received an initial 200-ml bolus of the study fluid over 2–4 min, and hemodynamic measurements were performed before and 3 min after the volume expansion. Thereafter, 100-ml boluses were infused over 2–4 min. The hemodynamic measurements were performed at 3 min after the completion of each bolus, and a new bolus was given immediately after the measurements, until SV did not increase more than 10 %.

In the prone position, measurements were performed at 5-min intervals during surgery. Further boluses of 100 ml of study fluid were given during surgery if SV decreased more than 10 % from the value obtained in the supine position. The patient was considered to be a non-responder if the SV did not increase with three consecutive boluses of study fluid in the prone position, and in such cases the volume expansion was stopped. Hemoglobin below the level of 10 g/dl was the trigger for red blood cell transfusion. Hemodynamic measurements were performed at the end of surgery and in the supine position. Postoperatively, all patients were given a basal infusion of RAC at a rate of 1 ml/kg/h until the following morning. In the prone position two longitudinal chest supports were used. The patient's head was placed on a headrest (Prone View® Protective Helmet System; Dupaco, Oceanside, CA, USA), or fixed with the Sugita pin head-holder device (Sugita® Head Frames; Mizuho America, Union City, CA, USA).

Patients were extubated either immediately after surgery or in the neurosurgical intensive care unit (NICU). All patients were followed up postoperatively at the NICU. Patient weight was registered on the day before surgery and on the first postoperative day.

Thromboelastometry

Thromboelastometry and hematology parameters were studied after the induction of anesthesia (Pre), after the total amount of boluses of the study infusion given in the supine position before positioning (Post), and at the end of surgery (End). Arterial blood gas samples were taken after the prone positioning. Blood samples for thromboelastometry were collected via a nonheparinized radial artery catheter into polypropylene tubes (BD Vacutainer®; BD Diagnostics, Plymouth, UK) containing 3.2 % buffered citrate. Modified thromboelastometry coagulation analysis (ROTEM®; Pentapharm, Munich, Germany) was carried out using four different tests [intrinsic ROTEM (contact coagulation activator, InTEM®); extrinsic ROTEM (tissue coagulation activator, ExTEM®); fibrinogen ROTEM (FibTEM®); aprotinin ROTEM (ApTEM®)]. With the FibTEM® test, platelet function is inhibited by cytochalasin D to prevent platelet aggregation. FibTEM® measures the strength of the fibrin component of the clot. ApTEM® identifies hyperfibrinolysis by addition of aprotinin to ExTEM®.

During the coagulation analysis, coagulation was initiated by recalcification (StarTEM®) and activators using a semi-automated electronic pipette system according to the manufacturer's instructions. Coagulation was allowed to proceed for 60 min. Automatically measured ROTEM® variables were clotting time (CT, s), clot formation time (CFT, s), α-angle (α, degree), and maximum clot firmness (MCF, mm). Arterial blood samples were analyzed for hemoglobin (Hb, g/dl), hematocrit (Hct, %), and platelet count (PC, 10^9/l) using Sysmex K-4500® (Sysmex, Kobe, Hyogo, Japan). Arterial blood gases were analyzed using Radiometer ABL825® (Radiometer, Copenhagen, Denmark).

Statistics

The study was designed to discover a threefold difference in the needed volume of study fluid (α-error = 5 %) between the groups. Study power was 80 %. On the basis of our previous study [9], the number of subjects per group is also sufficient to detect a difference of 15 % in MCF of the thromboelastometry. The results are reported as mean and standard deviation (SD), or 95 % confidence interval, or medians and range when the parameter is not normally distributed. In the figures we also used standard error of the mean (SEM). The Kolmogorov–Smirnov test was used for test of normality. The Mann–Whitney *U* test or the Wilcoxon signed-rank test was applied for paired comparisons between or within the groups, respectively. Differences within the groups over the time period were tested by analysis of variance (ANOVA) on rank. For hemodynamic parameters the analysis was done with a linear mixed model with subject specific random effects of time and time squared, to allow nonlinear variation in the individual trajectories. Time points were from 0 to 230 in 5-min intervals. We tested the interaction between linear, quadratic, and cubic time dependency using joint linear hypothesis of all effects being zero. $P < 0.05$ was considered statistically significant. The statistical calculations were carried out using SPSS (version 17.0), SigmaStat (version 2.03) for Windows software (SPSS, Chicago, IL, USA), or R-program (version 3.0.0) nlme package.

Results

A total of 35 patients were assessed for eligibility between November 2009 and May 2010 (Fig. 1). Two patients were excluded because of obesity (BMI >36), and in two cases the planned prone position was changed to a seated position before surgery. One patient refused consent. Overall 30 patients were included, and their data were analyzed by original assigned groups. One of the patients in the RAC-group needed a mannitol bolus because of inadequate brain relaxation. The data of this patient were analyzed until the administration of mannitol, applying the intention-to-treat principle. The perioperative characteristics of the patients (Table 1) were comparable in the two groups, with the exception of weight and body surface area (BSA). The patients in the RAC group had a higher weight and a

Fig. 1 Flowchart

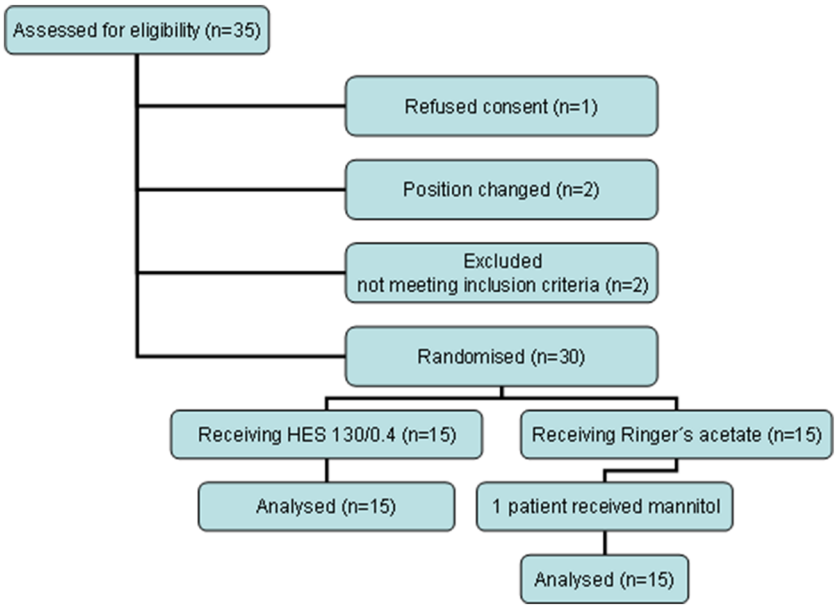

Table 1 Perioperative data

	HES $n = 15$	RAC $n = 15$
Gender (male/female)	4/11	9/6
Age (years)	55 ± 16	52 ± 20
Weight (kg)	70.9 ± 10.6	87.2 ± 15.1
Height (cm)	168 ± 8	172 ± 9
BSA (m^2)	1.8 ± 0.17	2.0 ± 0.22
ASA classification, I/II/III/IV	2/8/5/–	4/5/5/1
Type of anesthesia		
Sevoflurane	14	12
TIVA	1	3
Type of surgery		
Cervical	5	3
Lumbar	5	5
Thoracic	1	0
Chiari	4	4
Craniotomy	0	3
Duration of surgery (min)	169 ± 50	132 ± 63

Data are presented as numbers of patients (n) or mean ± SD

ASA American Society of Anesthesiologists, *BSA* body surface area, *HES* hydroxyethyl starch, *RAC* Ringer's acetate, *TIVA* total intravenous anesthesia

slightly higher BSA. The distribution of types of anesthesia and surgery did not differ significantly among the study groups. Also, the duration of surgery was comparable between the groups.

The mean dose of basal RAC infusion administered intraoperatively was 813 (235) and 868 (354) ml ($P = 0.620$) in the HES and RAC groups, respectively (Table 2). The mean cumulative doses of HES and RAC boluses before positioning were 240 (51) and 267 (62) ml ($P = 0.207$). All patients received the initial bolus of 200 ml fluid, but nine patients in the HES group and six in the RAC group did not need further boluses in the supine position. The mean cumulative dose of RAC boluses needed to optimize fluid filling was significantly higher at 30 min after the prone position ($P = 0.039$).

At the end of the surgery the mean (SD) cumulative doses of HES or RAC boluses were 440 (229) or 653 (368) ml ($P = 0.067$; 95 % confidence interval for difference of mean, −443–16 ml). Four patients were classified as non-responders and the volume expansion was stopped. In the RAC group, three (20 %) of the patients were non-responders, compared to one (6.7 %) in the HES group ($P = 0.598$). Intraoperative blood loss ($P = 0.861$), urine output ($P = 0.698$), and fluid balance ($P = 0.110$) were comparable in the two groups. There was no significant difference regarding weight gain ($P = 0.211$) between the groups. No diuretics were administered intraoperatively, other than to the one patient receiving mannitol.

HR or SVI did not differ between the groups during the entire study period. MAP increased more in the HES group over time ($P = 0.0002$). SVI increased in both HES and RAC groups during the prone position with no difference between groups ($P = 0.259$). CI increased in the HES group but not in the RAC group during the prone position; there was a difference between groups over time ($P = 0.015$) (Fig. 2). There were no significant differences between the groups regarding the total amount of vasoactives used, neither for phenylephrine ($n = 30$) [0.85 (0–6.6) and 0.68 (0–5.1) mg in the HES and RAC group, respectively, $P = 0.755$] nor for ephedrine ($n = 6$) [11.7

Table 2 Intraoperative fluid balance

	HES	RAC	*P* between groups	95 % confidence interval
Pre dose (ml)	240 ± 51	267 ± 62	0.207	−69 to 16
30-min dose (ml)	340 ± 124	453 ± 160	0.039	−220 to −6
End dose (ml)	440 ± 229	653 ± 368	0.067	−443 to 16
Total basal RAC dose (ml)	813 ± 235	868 ± 354	0.620	−280 to 170
Intraoperative blood loss (ml)	216 ± 160	201 ± 278	0.861	−155 to 184
Intraoperative urine output (ml)	352 ± 262	407 ± 480	0.698	−345 to 234
Intraoperative fluid balance (ml)	799 ± 305	1074 ± 569	0.110	−616 to 66

Cumulative amounts of the study fluids administered before the prone position (Pre), 30 min thereafter (30 min), and at the end of surgery (End). Values are mean ± SD. *t* test with 95 % confidence interval for difference of the mean of the amounts of fluid

HES hydroxyethyl starch, *RAC* Ringer's acetate

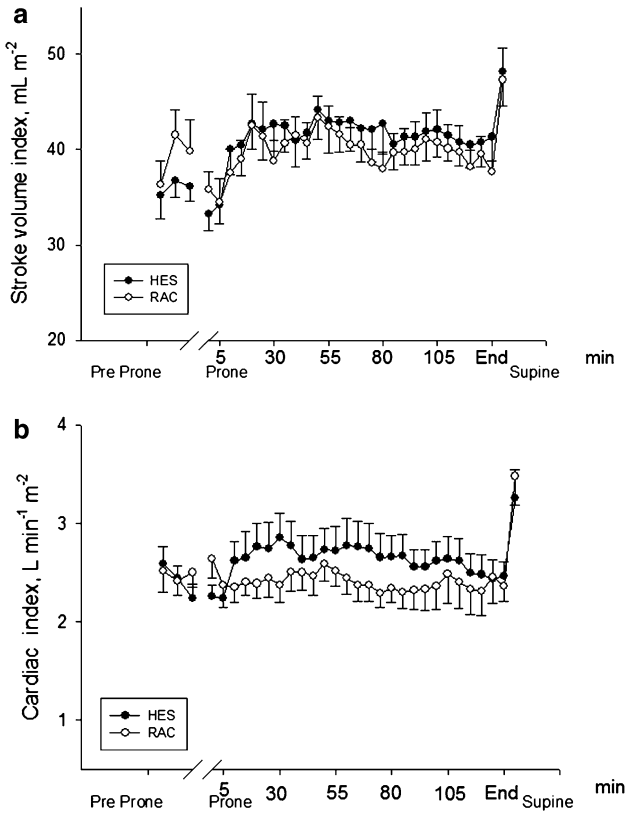

Fig. 2 Mean (SEM) stroke volume index (a) and cardiac index (b) before fluid filling, after fluid boluses before positioning, at 5-min intervals on prone position intraoperatively, and at the end of surgery, and on supine. *HES* hydroxyethyl starch, *RAC* Ringer's acetate

(5–15) and 6.7 (5–10) mg in the HES and RAC groups, respectively; $P = 0.239$]. Furthermore, there were no significant differences in the dose of phenylephrine during any time period during the study. End-tidal concentrations of inhaled sevoflurane were comparable between the groups 5 min after the positioning ($P = 0.107$), at 30 min after positioning ($P = 0.126$), and at the end of surgery ($P = 0.126$). Doses of the continuous infusion of propofol ($P = 0.768$), as well as the total dose of propofol ($P = 0.725$), were comparable between the groups. There was no difference in the total dose of fentanyl ($P = 0.653$), remifentanil ($P = 0.195$), or the amount of local anesthetics ($P = 0.348$) between the groups.

Table 3 Hematology results before (Pre), after boluses of study fluid (Post), and at the end of surgery (End)

	HES	RAC	*P* between groups
Hb (g/dl)			
Pre	12.7 ± 1.1	14.1 ± 1.3	0.005*
Post	11.9 ± 1.1#	13.3 ± 1.2#	0.002*
End	11.9 ± 0.9#	13.7 ± 1.2#	0.000*
Hct (%)			
Pre	36.4 ± 2.9	40.1 ± 3.3	0.003*
Post	33.9 ± 2.9#	37.8 ± 3.1#	0.001*
End	33.9 ± 2.3#	38.5 ± 3.2#	0.000*
Pc ($\times 10^9$)			
Pre	224.0 ± 75.5	203.1 ± 36.4	0.343
Post	204.1 ± 62.3#	193.6 ± 32.7#	0.569
End	218.3 ± 65.3	216.4 ± 43.4	0.925

Values are mean ± SD. *P* values are for *t* test

Hb hemoglobin, *Hct* hematocrit, *HES* hydroxyethyl starch, *Pc* platelet count, *RAC* Ringer's acetate

# $P < 0.05$ in comparison with Pre within the group (paired-samples *t* test)

*$P < 0.05$ HES in comparison with RAC (independent samples *t* test)

Hb and Hct values were slightly higher in the RAC group during the whole study period, but all values were within the normal laboratory reference range (Table 3). The baseline thromboelastometry parameters were comparable in the study groups (Table 4). In FibTEM analyses, α-angle ($P = 0.037$) and MCF ($P = 0.012$) decreased at the end of surgery in comparison with the baseline in the HES group. In the RAC group these parameters remained unchanged. One patient in the HES group received a transfusion of packed red blood cells during surgery because of

Table 4 ROTEM® results before (Pre), after boluses of study fluid (Post), and at the end of surgery (End)

	HES	RAC	*P* between groups
InTEM® MCF (mm)			
Pre	65.0 (57–70)	65.0 (58–76)	0.656
Post	65.0 (54–74)	64.0 (56–76)	0.682
End	65.0 (56–71)	67.0 (58–76)	0.167
InTEM® α-angle (°)			
Pre	77.0 (71–80)	76.5 (73–82)	0.802
Post	76.5 (72–78)	78.0 (73–83)	0.102
End	76.0 (72–79)	77.0 (73–82)	0.249
ExTEM® MCF (mm)			
Pre	61.0 (54–72)	62.5 (54–74)	0.780
Post	60.5 (52–70)	61.0 (54–75)	0.214
End	61.0 (53–73)	64.0 (57–76)	0.300
ExTEM® α-angle (°)			
Pre	75.0 (66–80)	73.5 (69–80)	0.560
Post	72.0 (63–78)#	74.0 (67–81)	0.325
End	73.0 (62–80)	75.0 (68–81)	0.436
FibTEM® MCF (mm)			
Pre	15.0 (11–25)	16.0 (9–28)	0.485
Post	14.5 (10–35)	15.5 (11–40)	0.732
End	13.0 (9–23)#	16.0 (10–31)	0.079
FibTEM® α-angle (°)			
Pre	70.0 (52–80)	68.5 (52–82)	0.954
Post	65.5 (59–81)	74.0 (51–82)	0.390
End	61.0 (32–77)#	73.0 (55–84)	0.016*
ApTEM® MCF (mm)			
Pre	62.0 (54–71)	65.0 (56–76)	0.196
Post	60.0 (54–78)	62.0 (54–75)	0.775
End	66.0 (55–72)	64.0 (57–78)	0.572
ApTEM® α-angle (°)			
Pre	76.0 (70–78)	75.0 (69–80)	0.568
Post	73.0 (69–80)#	74.0 (64–78)	0.786
End	74.0 (61–79)	75.0 (70–82)	0.678

Values are presented as median (range)

HES hydroxyethyl starch, *MCF* maximum clot firmness, *RAC* Ringer's acetate

* $P < 0.05$ HES in comparison with RAC (one-way ANOVA)

# $P < 0.05$ in comparison with Pre within the group (Friedman test, post hoc Tukey test)

intraoperative bleeding (450 ml). Neither platelet concentrate nor fresh frozen plasma was transfused intraoperatively.

The duration of postoperative ventilator treatment, ICU stay, and hospital stay were similar between the groups. The duration of postoperative mechanical ventilation, ICU stay, and hospital stay in the HES and RAC groups were 0 (0–2) h and 0 (0–1) h, 3.0 (1.5–22), and 5.5 (1.5–25) h, and 3 (1–6) and 3 (1–8) days respectively. There were no reoperations as a result of bleeding or for any other reason.

Discussion

This study of patients undergoing neurosurgery in the prone position demonstrates that the amount of RAC is 25 % higher than the amount of HES needed to achieve a comparable hemodynamic profile. Our results indicate that most of the patients undergoing neurosurgery in the prone position can be managed with a relatively small volume of RAC instead of HES, bearing in mind that even such small doses of HES may disturb blood coagulation.

The effects of HES 130/0.4 on hemostasis may be clinically relevant and should be investigated in prospective randomized trials with adequate statistical power. However, the observation of a significant increase in CI, within the HES group but not within the RAC group, might justify administration of HES according to the goal-directed principle in hypovolemic patients requiring instant restoration of hemodynamics. Then, the risk of excessive fluid load may be minimized.

Previous studies have shown impaired hemodynamics in the prone position during anesthesia. Prone positioning has been shown to decrease CO and CI [10]. The patient position, positioning device, and the pressure on the inferior vena cava affect the degree of the hemodynamic changes with prone positioning [11, 12]. In their study of various prone positions, Dharmavaram and coworkers [13] concluded that adequate volume resuscitation reduces changes in blood pressure and heart rate usually seen with prone positioning for spine surgery. They calculated the fluid deficit according to body weight and the time of preoperative fasting, and administered 75 % of the fluid deficit (mean volume given, 1,020–1,335 ml in the different prone positioning systems) before the induction of anesthesia. Despite fluid replacement, CI was reduced in the prone position during isoflurane anesthesia. In another study, Biais and coworkers [14] administered a bolus of 500 ml 6% hetastarch before positioning according to the estimation of fluid responsiveness with Vigileo®/FloTrac® stroke volume variation (SVV), but a significant decrease in CO was noted in the prone position. In contrast to earlier studies, our study shows that fluid optimization before the prone positioning prevents position-induced CO decrease.

In the current study, fluid administration before prone positioning was based on optimizing the stroke volume, as previously described. All the patients were fasting for 6 h preoperatively. Jacob and coworkers concluded in their study that the blood volume is normal after preoperative overnight fasting [15]. Stroke volume variation (SVV)

measurement by the Vigileo®/FloTrac® has been shown to be a good indicator of fluid responsiveness in mechanically ventilated patients [16–19]. The diagnostic value of stroke volume variation in predicting fluid responsiveness is good with an AUC of 0.84 [20]. SVV measurement (PiCCO®) and pulse pressure variation (PPV) have also been demonstrated to be reliable predictors of fluid responsiveness in patients undergoing brain surgery [21, 22]. In the present study we found that the volumes needed for optimal fluid filling before prone positioning (i.e. 240 ml HES or 267 ml RAC) were much less than those reported by Biais et al. (500 ml HES) [14] or by Dharmavaram and coworkers (mean volume given 1,020–1,335 ml) [13]. The total volume of fluids given in our study (mean, 1,253 and 1,521 ml in the HES and RAC groups, respectively) was also relatively small. Optimal perioperative fluid administration minimizes the risk of excessive tissue edema and weight gain [23, 24]. Especially, patients with a disrupted blood–brain barrier are vulnerable to brain edema during liberal fluid resuscitation [25]. It has been suggested that an increment of only 13 ml brain water content may be catastrophic to an adult patient whose intracranial compensation mechanisms are already exhausted [26]. Excessive fluid administration may also cause edema of the optic nerve and contribute to the development of posterior ischemic optic neuropathy postoperatively [27].

Many studies have compared colloid and crystalloid fluid therapy in a variety of clinical settings [28–30], but there is still controversy on this issue. It is commonly believed that two to three times more crystalloid than colloid fluid is needed to restore and maintain filling pressures in the treatment of hypovolemia [31]. Recent studies have shown that the ratio between required volumes in the crystalloid and colloid groups is in fact more in a range between one and two [32]. Our findings support these observations, but it should be kept in mind that the hemodynamic response of fluid administration is largely dependent on the combined effect of the degree of hypovolemia, dosing regimen, and the type of the fluid. The patients in this study had a short fasting period preoperatively, and their intraoperative blood loss was minimal. Two earlier studies comparing the effect of HES and a crystalloid on hemodynamics after cardiac or vascular surgery have shown better effect of fluid challenge with HES than saline or RAC on cardiac and stroke volume index [31, 33]. Although more scientific evidence of colloids versus crystalloids is needed, some studies suggest that colloid resuscitation may result in less peripheral edema [23, 24] and better quality of recovery in the postoperative period [34, 35]. Furthermore, some experimental studies show that a decrease in plasma colloid oncotic pressure, in addition to decreasing plasma osmotic pressure, may aggravate cerebral edema [36].

The adverse effects of HES solutions on coagulation have limited their use in neurosurgery [37]. The HES-associated coagulopathy is dose dependent [38]. Hydroxyethyl starches of lower MW and molar substitution have fewer adverse effects on coagulation and hemostasis and have been used in patients with severe head injury [39]. Even rapidly degradable HES solutions (6 % HES 130/0.4) has been shown to impair fibrin formation and clot strength in thromboelastometry after cardiac surgery [40]. Our results of decreased formation and maximum strength of the fibrin clot in the HES group, but not in the RAC group, are in accordance with these earlier results. The clinical relevance of these findings remains unclear, because the frequency of bleeding in these patients was very low and only one patient in the HES group needed transfusion of packed red blood cells during surgery.

There are limitations in this study. We were unable to blind the anesthesiologists as to the treatment group and hence may have introduced bias. However, intraoperative fluid administration in both groups was guided by specific fluid administration protocols, which should minimize bias. The anesthetic induction and maintenance were not totally standardized. For induction of anesthesia we used two different anesthetics (thiopental, and propofol) as a result of problems in the distribution of thiopental during the study period. Four of the 30 patients received TIVA, 3 because of increased risk for postoperative nausea and vomiting (PONV) and 1 because of a large intracranial tumor. However, there were no differences in anesthetic dose or vasoactives given during surgery between the groups. According to a study by Sudheer et al. [41], there could be a greater change in CO during maintenance of anesthesia using propofol compared to isoflurane. However, in our study the distribution of different types of anesthesia, and different types of surgery, did not differ significantly among the study groups. The patients in the RAC group had a higher weight and higher BSA, and therefore we chose to report the cardiac parameters as CI and SVI. The basal infusion of RAC was 3 ml/kg/h for all patients, and here the difference in weight between the groups could have caused bias. However, there was no difference in the total dose of basal RAC between the groups. The hemoglobin level was lower, although in the normal range, in the HES group from the beginning of the study period. It is unlikely that this slight hemodilution could alter the coagulation parameters. Thromboelastometry was not followed up after the surgery, but there were no bleeding complications postoperatively.

In summary, we conclude that to achieve comparable hemodynamic profiles in the study groups, the amount of RAC was 25 % higher than the amount of HES, which is lower than previously reported. With careful titration and monitoring of either RAC or HES volume, such as SV-

directed administration of fluids, it is possible to maintain a stable circulatory state in the prone position during neurosurgery. Most of the patients undergoing neurosurgery in the prone position can be managed with an acceptable volume of RAC instead of HES. However, HES may be administered when fluid volume should be minimized and instant restoration of intravascular volume is indicated.

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Conflict of interest Tomi Niemi has received honoraria for lecturing from Fresenius Kabi Ab, and Bayer Health Care, Finland, and an educational grant from Leo Pharma, Finland. For the remaining authors, no conflicts were declared.

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